### VECTICAL® (calcitriol) Ointment
**For topical use only.**
Not for oral, intramuscular, or intravenous use. Not to be applied to the eyes, lips, or facial skin.

#### BRIEF SUMMARY
**Indication for Use**: VECTICAL Ointment is a Vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years of age and older.

#### CONTRAINDICATIONS
None

#### WARNINGS AND PRECAUTIONS
**Effects of Calcitriol on Calcium Metabolism**
In controlled clinical trials with VECTICAL Ointment, among subjects having laboratory monitoring, hypercalcemia was observed in 24% (178/745) of subjects exposed to active drug and in 16% (123/770) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were generally mild and transient. If alterations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with concomitant use of Ursodiol or Lithium Carbonate.

**Ultraviolet Light Exposure**
Animal data suggest that the vehicle of VECTICAL Ointment may enhance the ability of ultraviolet radiation (UV) to induce skin tumors. Subjects receiving topical VECTICAL Ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sunlamps. Physicians may wish to limit or avoid use of phototherapy in patients who use VECTICAL Ointment.

#### UNLEVIATED USES
The safety and effectiveness of VECTICAL Ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated. The safety and effectiveness of VECTICAL Ointment in patients with nephrostone disease, parathyroid disease, or postmenopausal osteoporosis has not been evaluated.

#### ADVERSE REACTIONS
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

##### Clinical Studies Experience:
VECTICAL Ointment was studied in two vehicle-controlled studies (419 subjects), and in one open label study (324 subjects). The table below describes exposure to VECTICAL Ointment in 419 subjects, including 239 exposed for 6 months and 116 exposed for 1 year.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>VECTICAL Ointment</th>
<th>Vehicle Ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Among subjects having laboratory monitoring, hypercalcemia was observed in 24% (178/745) of subjects exposed to active drug and in 16% (123/770) of subjects exposed to vehicle, however the elevations were less than 10% above the upper limit of normal. The open label study enrolled 324 subjects with psoriasis who were then treated for up to 52 weeks. Adverse events reported at a rate of greater than or equal to 3% of subjects treated with VECTICAL Ointment were lab test abnormality (8%), vitamin D (4%), hypercalcemia (3%), and pruritus (2%). Kidney stones were reported in 3 subjects and confirmed in 2. Phlebitis and keratitis were reported in 1 subject each.

The following adverse reactions have been identified during worldwide post-approval use of VECTICAL Ointment. Acute blisters, dermatitis, erythema, pain, pruritus, skin burning sensation, and skin discoloration. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### DRUG INTERACTIONS
VECTICAL Ointment should be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

Teratogenic Effects: Pregnancy Category C.
VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies in pregnant women. VECTICAL Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

#### Nursing Mothers
VECTICAL Ointment contains calcitriol. Because the safety and effectiveness of VECTICAL Ointment in nursing mothers are not known, it is not known whether the VECTICAL Ointment is excreted in human milk. Caution should be exercised when VECTICAL Ointment is administered to a nursing woman.

#### Pediatric Use
VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. Safety and effectiveness in pediatric patients have not been established.

#### Geriatrics
VECTICAL Ointment was studied in elderly patients (aged 65 and older) in two studies. No specific differences in responses between the elderly and younger patients were observed.

#### OVERDOSAGE
Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects.

#### NONCLINICAL TOXICOLOGY

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
When calcitriol was applied topically to mice for up to 24 months, no significant changes in tumor incidence were observed. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. A two-year carcinogenicity study was conducted in which calcitriol was orally administered to rats at dosages of approximately 0.005, 0.03, and 0.1 mcg/kg/day (0.05, 0.6, and 1.0 mcg/m²/day, respectively). The incidence of benign pleural mesotheliomas was significantly increased in female rats. No other significant differences in tumor incidence data were observed.

**Reproductive Toxicology**
Calcitriol showed lack of effect on reproductive performance of male rats exposed to up to 20 μg/kg/day of calcitriol. Concentrations of calcitriol in ointment vehicle of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. These data suggest that the vehicle of VECTICAL Ointment may enhance the ability of UVR to induce skin tumors. Calcitriol did not elicit genotoxic effects in the mouse lymphoma TK locus assay.

**Calcium Metabolism**
Administration of calcitriol to rats, dogs and monkeys at maximum tolerated dose in an expandable clinical trial did not result in any effect on serum calcium levels. In the long term, administration of calcitriol at 1 μg/kg/day (7 μg/m²/day) indicated no impairment of fertility or general reproductive performance. Based upon the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

**Ossification of the Pubic Bones**
A slightly increased incidence of skeletal variation was observed in the offspring of the nine responders who had M1c disease, but there was no clear dose related effect. This should be gently rubbed into the skin so that no medication remains on the hands. It is important to avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sunlamps.

### REFERENCES

1. Data on file, Galderma Laboratories, L.P.

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**BRAF, KIT-Mutation Targeters Offer Hope**

**By Patrice Wendling**

**Orlando** — The concept of targeted therapies in melanoma took a step closer to reality with two early trials reporting positive responses to agents that specifically target BRAF or KIT mutations.

In a phase I study of 55 patients with a variety of cancers, 21 metastatic melanoma patients were treated twice daily with at least 240 mg PLX4032, an investigational oral, small-molecule inhibitor that selectively targets the BRAF V600E kinase mutation occurring in most melanomas.

Partial responses by RECIST (Response Evaluation Criteria in Solid Tumors) were confirmed in 9 of 16 BRAF V600E mutation-positive tumors. Of the nine responders had M1c disease, the highest “m” stage, said Dr. Keith Flaherty and his associates reported at the annual meeting of the American Society of Clinical Oncology.

Seven patients developed disease progression at 3-14 months while still on therapy. A preliminary analysis suggests a progression-free survival of about 6 months, but the data are very immature and the trial is likely to change with longer follow-up, said Dr. Flaherty of the University of Pennsylvania, Philadelphia.

In contrast, no tumor regression was observed in the five melanoma patients lacking the BRAF mutation, and all developed progressive disease within the first 3 months.

Initial results from a second phase II study of imatinib in inoperable mela-
noma showed that a KIT mutation or amplification was present in 21% (31 of 146 tumors) screened. Thus far, 15 of the 31 patients, median age 71 years, have been treated with 400 mg imatinib twice daily on a continuous basis.

Of the 12 patients evaluated for response, the overall rate was 33% by RE-
CIST and included two complete re-

By Patrice Wendling

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**References**

1. Data on file, Galderma Laboratories, L.P.